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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

8/18

Office Action Summary	Application No.	Applicant(s)	
	09/532,708	JAIN ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-24,28,33,49 and 52-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-24,28,33,49 and 52-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed March 11, 2004. Claims 12-24, 28, 33 and 49 were previously pending. Applicants amended claims 12 and 33 and added new claims 52-64. Claims 12-24, 28, 33, 49 and 52-64 will be examined.

2. Applicant's arguments with respect to claims 12-24, 28, 33 and 49 have been considered but are moot in view of the new ground(s) of rejection.

Priority

3. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 12-24, 28, 33, 49 and 52-64 of this application. The provisional application No. 60/125,536, filed March 22, 1999, does not provide support for automated isolating and cloning of nucleic acids using robotic systems. Therefore the priority date of these claims is March 22, 2000, the filing date of the instant application.

Claim interpretation

4. Before proceeding with the rejection some of the terms used in the claims will be interpreted.

A) The term "a library of target nucleic acid(s)" (claim 12) is interpreted as meaning any target nucleic acid, since Applicants did not define this term in the specification.

B) The term "a library of target nucleic acid variants" (claim 19) is interpreted as meaning any nucleic acid obtained by homologous recombination with target nucleic acid, since Applicants did not define this term in the specification.

C) The term "library of candidate agents" in claim 21 is interpreted as one or more agents of any origin.

D) A definition of separation moiety is provided by Applicants (page 22, lines 21-28):

“By "separation moiety" or “purification moiety" or grammatical equivalents herein is meant a moiety which may be used to purify or isolate thenucleic acids, including the targeting polynucleotides, the targeting polynucleotidertarget sequence complex, or the target sequence. As will be appreciated by those in the art, the separation moieties may comprise any number of different entities, including, but not limited to, haptens such as chemical moieties, epitope tags, binding partners, or unique nucleic acid sequences, basically anything that can be used to isolate or separate a targeting polynucleotide:target sequence complex from the rest of the nucleic acids present.”

E) Applicants did not define the term ”an automated transformation system”, therefore it is interpreted as any device which performs cell transformation.

F) Applicants did not define the term ”a bead picker”, therefore it is interpreted as any device which performs the function of picking up beads.

G) Applicants did not define the term ”an incubator”, therefore it is interpreted as any device which performs incubation of samples.

Claim Rejections - 35 USC § 103

5. Claims 12-20, 28, 33, 49, 53, 56, 58, 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pati et al. (U.S. Patent No. 6,524,856; cited in the previous office action) and Cathart et al. (WO 91/16675; cited in a previous office action), in view of Van Nostrand’s Scientific Encyclopedia (7^{th} Edition, Considine, D.M., Editor; Van Nostrand Reinhold, New York, 1989).

A) Regarding claim 12, Pati et al. teach a method for targeting sequence modifications in a family of genes using homologous recombination (Abstract). In particular, Pati et al. teach a method comprising the steps

a) providing a plurality of enhanced homologous recombination (EHR) compositions, wherein each composition comprises:

i) a recombinase (Pati et al. teach coating of double stranded (ds) DNA probes with recombinase (Fig. 2; col. 8, lines 1-3; col. 12, lines 32-36; col. 16, lines 16-37));

ii) a first and a second targeting polynucleotide, wherein said first targeting polmucleotide comprises a portion substantially complementary to a fragment of a target nucleic acid and is substantially complementary tosaid second targeting polynucleotide (Pati et al. teach a plurality of EHR compositions comprising target nucleic acids from a mixture of nucleic acids, two-single stranded targeting polynucleotides which are substantially complementary to each other and each has a homology clamp (= a portion substantially complementary to a fragment of a target nucleic acid) for target nucleic acids from a gene family; see col. 4, lines 31-37; col. 13, lines 11-16 and 35-45; col. 14, lines 15-21 and 64-67); and

iii) a separation moiety (Pati et al. teach targeting polynucleotides with attached purification tags; see col. 4, lines 37-42;col. 23, lines 9-14; col. 26, lines 1-13);

b) contacting said EHR compositions with a library of target nucleic acid(s) under conditions wherein said targeting polynucleotides hybridize to one or more target nucleic acids of said library (Pati et al. teach contacting EHR compositions with a library of target nucleic acids; see Fig. 2; col. 30, lines 1-5); and

c) isolating and cloning said target nucleic acid(s) (Pati et al. teach isolation of the target nucleic acids by binding biotin to targeting polynucleotides and isolating target nucleic acid: targeting polynucleotide complex using streptavidin-coated magnetic beads and cloning of the isolated genes (Fig. 2; col. 23, lines 9-14; col. 25, lines 52-58; col. 26, lines 1-13).).

Regarding claim 13, Pati et al. teach target nucleic acid being a target gene (col. 6, lines 47, 48; col. 25, lines 41-67; col. 26, lines 1-13 and 31-39).

Regarding claim 14, Pati et al teach target nucleic acid being a portion of a target gene, such as sequence encoding a protein domain (col. 6, lines 54-56; col. 13, lines 35-38).

Regarding claim 15, Pati et al. teach target nucleic acid being a regulatory sequence (col. 6, lines 47-50; col. 19, lines 19-33).

Regarding claim 16, Pati et al. teach target nucleic acids comprising disease allele (col. 29, lines 1-19). Pati et al. do not specifically teach single-nucleotide polymorphisms, but since a disease allele means a nucleic acid sequence which differs by at least one nucleotide from a wild-type sequence, single nucleotide polymorphisms are inherently disease alleles, therefore Pati et al. teach target nucleic acids comprising single-nucleotide polymorphisms.

Regarding claim 17, Pati et al. teach cDNA libraries (Fig. 2; col. 26, line6; col. 30, line 4), genomic DNA samples (col. 6, lines 47-54 and 61-64).

Regarding claims 18 and 49, Pati et al. teach germline and pathogen target sequences (col. 6, lines 61-64).

Regarding claim 19, Pati et al. teach making a library of variant nucleic acids by introduction of alterations in the target nucleic acids (col. 17, lines 29-67; col. 18, lines 14; col. 26, lines 14-30), introducing the library of nucleic acid variants into cellular library (col. 26, lines 40-67; col. 27, 28) and performing phenotypic screening on the cellular library (col. 29, lines 22-29).

Regarding claim 28, Pati et al. teach sequencing of target nucleic acids (col. 25, lines 59-60; col. 26, lines 12, 13).

B) Pati et al. teach that the recombination composition can be used for cloning of genes (col. 25, lines 50, 51), creating pools of libraries of variant nucleic acid sequences and cellular libraries

containing the variant libraries (col. 26, lines 24-30). Pati et al. teach identification of colonies which contain the desired inserts and screening the colonies by sequencing (col. 30, lines 6-14). Pati et al. do not teach using a robotic system for isolating and cloning target nucleic acids, where the system comprises computer processor programmed to manipulate a device comprising at least one of a gene sequencer, a bead picker, an incubator.

C) Regarding claims 12, 20 and 33, Cathcart et al. teach a robotic system for performing molecular biology procedures comprising a liquid-handling instrument with a modular stations to support liquid containers, automated pipettor, heating and cooling stations, thermocycler and a magnetic separation station for performing DNA isolation, all controlled by a computer system (Abstract; page 6, third paragraph; page 7; page 8, paragraphs 1 and 2; Fig. 1; page 10-15; page 23, paragraphs 3, 4; page 24; page 25, paragraphs 1 and 2; page 47, second paragraph).

Specifically, regarding claims 12, 33 and 53, Cathcart et al. teach a computer-controlled automated sequencer (page 47, second paragraph).

Regarding claims 12, 33 and 56, Cathcart et al. teach a magnetic separation station, which is used to handle paramagnetic beads (Fig. 1; page 11, second paragraph; page 13, second paragraph; page 23; page 23, last two paragraphs; page 24; page 25, first three paragraphs).

Regarding claims 12, 33 and 58, Cathcart et al. teach an inubator, which allows keeping samples at predermined temperatures (page 7, last paragraph; page 8, first paragraph; page 11, last paragraph; page 12, third paragraph).

Regarding claims 12, 33, 60 and 61, Cathcart et al. teach a fluorescent detection of the gel image from the gel sequencer (page 47, second paragraph). Cathcart et al. do not specifically teach teach a spectrofluorimeter (= spectrofluorometer) or a spectrophotometer. As evidenced by Van Nostrand's Scientific Encyclopedia, spectrofluorometer is a spectrophotometer which provides

means for both controlling the exciting wavelength and for identifying and measuring light output of a fluorescing sample. Therefore, since both laser excitation and fluorescent detection were used in the acqusition of gel image described by Cathcart et al., Cathcart et al. inherently teach a spectrofluorometer and a spectrophotometer.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the robotic system of Cathcart et al. in a method of Pati et al. The motivation to do so, provided by Cathcart et al., would have been that robotic system provided genetic information from a DNA sample overnight, as compared to days (page 49, the last paragraph). As stated by Cathcart ".... it is concluded that a robotic liquid handling instrument according to the invention can be used successfully to automate specific human gene detection ... The manner of which this result is accomplished is simpler and faster than the manual methods typically employed. The individual liquid handling steps are executed with precision. Since operation is computer controlled the process can be performed consistently, reliably, and relentlessly providing a new opportunity for high sample throuput." (page 50, first paragraph).

In addition, as stated in MPEP 2144.04 [R-1], automating manual activity is not sufficient to distinguish over the prior art.

2144.04 [R-1] III. AUTOMATING A MANUAL ACTIVITY

> In re Venner, 262 F.2d 91, 95, 120 USPQ 193, 194 (CCPA 1958) (Appellant argued that claims to a permanent mold casting apparatus for molding trunk pistons were allowable over the prior art because the claimed invention combined "old permanent-mold structures together with a timer and solenoid which automatically actuates the known pressure valve system to release the inner core after a predetermined time has elapsed." The court held that broadly providing an automatic or mechanical means to replace a manual activity which accomplished the same result is not sufficient to distinguish over the prior art.).

6. Claims 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pati et al. (U.S. Patent No. 6,524,856) and Cathart et al. (WO 91/16675; cited in a previous office action) in view of

Van Nostrand's Scientific Encyclopedia (7th Edition, Considine, D.M., Editor; Van Nostrand Reinhold, New York, 1989), as applied to claim 12 above, and further in view of Ghai et al. (U.S. Patent No. 5,955,269; cited in a previous office action).

A) Regarding claim 21, Pati et al. teach identification of novel target genes which can be used in screening of drug candidates (col. 25, lines 64-67) and making a plurality of target cells comprising mutant target nucleic acids (col. 26, lines 14-30 and 40-67; col. 27, 28).

Regarding claim 23, Pati et al. teach mutant target nucleic acids being a sequence knock-out (col. 17, lines 46-60; col. 25, lines 41-51).

Regarding claim 24, Pati et al. teach mutant target nucleic acids comprising insertions, deletions or combinations thereof (col. 18, lines 10-67; col. 19, lines 1-18).

Regarding claim 22, Cathcart et al. teach a robotic system for performing molecular biology procedures comprising a liquid-handling instrument with a modular stations to support liquid containers, automated pipettor, heating and cooling stations, thermocycler and a magnetic separation station for performing DNA isolation, all controlled by a computer system (Abstract; page 6, third paragraph; page 7; page 8, paragraphs 1 and 2; Fig. 1; page 10-15; page 23, paragraphs 3, 4; page 24; page 25, paragraphs 1 and 2).

B) Neither Pati et al. nor Cathcart et al. teach adding a library of candidate agents to the cells and determining the effect of candidate agents on the cells.

B) Regarding claim 21, Ghai et al. teach methods of screening for the presence of bioactive substances in food (= library of candidate agents) by testing for their ability to modify gene expression in cells in vitro (col. 2, lines 51-67) or in animal models (col. 3, lines 1-15). The assays measure expression of genes (col. 3, lines 66-67; col. 4, lines 1-12) or determine phenotypic

changes in cells (col. 4, lines 33-39). Once the effects of the active compound have been determined, the compound can be isolated and purified (col. 4, lines 44-50).

Regarding claim 22, Ghai et al. teach that the cells can be cultured and assayed using a robotic device (col. 17, lines 18-30).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the robotic system of Cathcart et al. in a method of Pati et al. The motivation to do so, provided by Cathcart et al., would have been that robotic system provided genetic information from a DNA sample overnight, as compared to days (page 49, the last paragraph). As stated by Cathcart ".... it is concluded that a robotic liquid handling instrument according to the invention can be used successfully to automate specific human gene detection ... The manner of which this result is accomplished is simpler and faster than the manual methods typically employed. The individual liquid handling steps are executed with precision. Since operation is computer controlled the process can be performed consistently, reliably, and relentlessly providing a new opportunity for high sample throuput." (page 50, first paragraph).

In addition, as stated in MPEP 2144.04 [R-1], automating manual activity is not sufficient to distinguish over the prior art.

2144.04 [R-1] III. AUTOMATING A MANUAL ACTIVITY

> In re Venner, 262 F.2d 91, 95, 120 USPQ 193, 194 (CCPA 1958) (Appellant argued that claims to a permanent mold casting apparatus for molding trunk pistons were allowable over the prior art because the claimed invention combined "old permanent-mold structures together with a timer and solenoid which automatically actuates the known pressure valve system to release the inner core after a predetermined time has elapsed." The court held that broadly providing an automatic or mechanical means to replace a manual activity which accomplished the same result is not sufficient to distinguish over the prior art.).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used the combined method of Cathcart et al. and Pati et al. to screen for candidate

agents of Ghai et al. The motivation to do so, provided by Ghai et al., would have been that candidate agents determined in food were used to treat or prevent disease (Abstract; col. 2, lines 35-48).

7. Claims 12, 33 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pati et al. (U.S. Patent No. 6,524,856) and Cathart et al. (WO 91/16675; cited in a previous office action) in view of Frank et al. (Biotechnology, vol. 6, pp. 1211-1213, 1988).

A) Regarding claim 12, Pati et al. teach a method for targeting sequence modifications in a family of genes using homologous recombination (Abstract). In particular, Pati et al. teach a method comprising the steps

a) providing a plurality of enhanced homologous recombination (EHR) compositions, wherein each composition comprises:

i) a recombinase (Pati et al. teach coating of double stranded (ds) DNA probes with recombinase (Fig. 2; col. 8, lines 1-3; col. 12, lines 32-36; col. 16, lines 16-37));

ii) a first and a second targeting polynucleotide, wherein said first targeting polmucleotide comprises a portion substantially complementary to a fragment of a target nucleic acid and is substantially complementary tosaid second targeting polynucleotide (Pati et al. teach a plurality of EHR compositions comprising target nucleic acids from a mixture of nucleic acids, two-single stranded targeting polynucleotides which are substantially complementary to each other and each has a homology clamp (= a portion substantially complementary to a fragment of a target nucleic acid) for target nucleic acids from a gene family; see col. 4, lines 31-37; col. 13, lines 11-16 and 35-45; col. 14, lines 15-21 and 64-67); and

iii) a separation moiety (Pati et al. teach targeting polynucleotides with attached purification tags; see col. 4, lines 37-42;col. 23, lines 9-14; col. 26, lines 1-13);

b) contacting said EHR compositions with a library of target nucleic acid(s) under conditions wherein said targeting polynucleotides hybridize to one or more target nucleic acids of said library (Pati et al. teach contacting EHR compositions with a library of target nucleic acids; see Fig. 2; col. 30, lines 1-5); and

c) isolating and cloning said target nucleic acid(s) (Pati et al. teach isolation of the target nucleic acids by binding biotin to targeting polynucleotides and isolating target nucleic acid: targeting polynucleotide complex using streptavidin-coated magnetic beads and cloning of the isolated genes (Fig. 2; col. 23, lines 9-14; col. 25, lines 52-58; col. 26, lines 1-13).).

B) Pati et al. teach that the recombination composition can be used for cloning of genes (col. 25, lines 50, 51), creating pools of libraries of variant nucleic acid sequences and cellular libraries containing the variant libraries (col. 26, lines 24-30). Pati et al. teach identification of colonies which contain the desired inserts and screening the colonies by sequencing (col. 30, lines 6-14). Pati et al. do not teach using a robotic system for isolating and cloning target nucleic acids, where the system comprises computer processor programmed to manipulate a device comprising at least one of a gene loader, a gene sequencer or an incubator.

C) Regarding claims 12 and 33, Cathcart et al. teach a robotic system for performing molecular biology procedures comprising a liquid-handling instrument with a modular stations to support liquid containers, automated pipettor, heating and cooling stations, thermocycler and a magnetic separation station for performing DNA isolation, all controlled by a computer system (Abstract; page 6, third paragraph; page 7; page 8, paragraphs 1 and 2; Fig. 1; page 10-15; page 23, paragraphs 3, 4; page 24; page 25, paragraphs 1 and 2; page 47, second paragraph).

Specifically, regarding claims 12 and 52, Cathcart et al. teach a computer-controlled automated sequencer (page 47, second paragraph).

D) Neither Pati et al. nor Cathcart et al. teach a gel loading system.

E) Frank et al. teach a workstation for a micromanipulation of liquids, which is a computer controlled (page 1212, last paragraph; page 1213, first paragraph) system consisting of a robotic arm, multichannel liquid dispenser, temperature-controlled incubators and the dispensing probe (Fig. 1). The system can be used to automate sequencing reactions, for example, in sequencing cloned DNA (page 1213, third paragraph). The sequencing reactions were robotically loaded onto a sequencing gel (page 1213, fourth paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the automatic system with gel loader of Frank et al. in the method of Pati et al. and Cathcart et al. The motivation to do so, provided by Frank et al., would have been that cloning could be performed with "improved precision and excellent reproducibility" by an automated instrument (page 1211, first paragraph). Further, as stated by Frank et al. "Due to the reproducible reaction conditions and due to the simultaneous addition of reagents to the four tracks of the sequencing reaction a highly uniform band density is obtained. This feature and the automation of the gel loading process make the workstation an ideal complement to automated gel reading apparatus, allowing the total automation of the sequencing process." (page 1213, last paragraph).

8. Claims 12, 33, 55 and 60-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pati et al. (U.S. Patent No. 6,524,856) and Bylina et al. (U.S. Patent No. 5,914,245).

A) Regarding claim 12, Pati et al. teach a method for targeting sequence modifications in a family of genes using homologous recombination (Abstract). In particular, Pati et al. teach a method comprising the steps

a) providing a plurality of enhanced homologous recombination (EHR) compositions, wherein each composition comprises:

i) a recombinase (Pati et al. teach coating of double stranded (ds) DNA probes with recombinase (Fig. 2; col. 8, lines 1-3; col. 12, lines 32-36; col. 16, lines 16-37));

ii) a first and a second targeting polynucleotide, wherein said first targeting polmucleotide comprises a portion substantially complementary to a fragment of a target nucleic acid and is substantially complementary to said second targeting polynucleotide (Pati et al. teach a plurality of EHR compositions comprising target nucleic acids from a mixture of nucleic acids, two-single stranded targeting polynucleotides which are substantially complementary to each other and each has a homology clamp (= a portion substantially complementary to a fragment of a target nucleic acid) for target nucleic acids from a gene family; see col. 4, lines 31-37; col. 13, lines 11-16 and 35-45; col. 14, lines 15-21 and 64-67); and

iii) a separation moiety (Pati et al. teach targeting polynucleotides with attached purification tags; see col. 4, lines 37-42;col. 23, lines 9-14; col. 26, lines 1-13);

b) contacting said EHR compositions with a library of target nucleic acid(s) under conditions wherein said targeting polynucleotides hybridize to one or more target nucleic acids of said library (Pati et al. teach contacting EHR compositions with a library of target nucleic acids; see Fig. 2; col. 30, lines 1-5); and

c) isolating and cloning said target nucleic acid(s) (Pati et al. teach isolation of the target nucleic acids by binding biotin to targeting polynucleotides and isolating target nucleic acid: targeting polynucleotide complex using streptavidin-coated magnetic beads and cloning of the isolated genes (Fig. 2; col. 23, lines 9-14; col. 25, lines 52-58; col. 26, lines 1-13).).

B) Pati et al. teach that the recombination composition can be used for cloning of genes (col. 25, lines 50, 51), creating pools of libraries of variant nucleic acid sequences and cellular libraries containing the variant libraries (col. 26, lines 24-30). Pati et al. teach identification of colonies which contain the desired inserts (col. 30, lines 6-14). Pati et al. do not teach using a robotic system for isolating and cloning target nucleic acids, where the system comprises computer processor programmed to manipulate a device comprising at least one of a colony picker, a spectrofluorimeter, a spectrophotometer, a luminometer or a CCD camera.

C) Bylina et al. teach automation of colony screening procedure for detection of colonies of cells expressing mutated enzymes by using MicroColonyImager (Abstract). The instrument can be used for high-throughput screening of libraries expressing mutagenized enzymes, for massively parallel screening of enzymes undergoing direct evolution or for high-throughput screening of recombinant DNA libraries (col. 3, lines 50-54).

Regarding claims 12, 33 and 55, Bylina et al. teach a computer-controlled system comprising a colony picker (col. 5, lines 62-67; col. 6, lines 1-15; col. 7, lines 29-43; Fig. 2).

Regarding claims 12, 33, 60 and 61, Bylina et al. teach a computer-controlled system comprising a spectrophotometer/fluorimeter (col. 3, lines 55, 56; col. 4, lines 30-44; col. 6, lines 58-67; col. 7, lines 29-43; Fig. 2).

Regarding claims 12, 33 and 62, Bylina et al. teach detection of chemiluminescence (col. 10, lines 58-64). Bylina et al. do not specifically teach a luminometer, but since they teach detection of luminescence, the spectrophotometer is inherently also a luminometer.

Regarding claim 63, Bylina et al. teach a CCD camera (col. 5, lines 37-61).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the automatic system with colony picker of Bylina et al. in the method of

Pati et al. The motivation to do so, provided by Bylina et al., would have been that "Use of the instrument can lead to the isolation of variant enzymes having activities which are commercially useful for the organic/biochemical synthesis of various substances, including chiral pharmaceuticals" (col. 3, lines 56-60).

9. Claims 54 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pati et al. (U.S. Patent No. 6,524,856; cited in a previous office action) and Bylina et al. (U.S. Patent No. 5,914,245), as applied to claim 12 above, and further in view of Unger et al. (U.S. Patent No. 6,627,421).

A) The teachings of Pati et al. and Bylina et al. are described above. Neither Pati et al. nor Bylina et al. teach automated transformation system.

B) Unger et al. teach a robotic system for cell transformation, the system comprising a computer, a plurality of acoustic probes for applying energy to cells and a robot (col. 2, lines 53-65; Fig. 1; col. 5, lines 50-60). The system is used to deliver nucleic acids to the interior of cells (col. 8, lines 56-65; col. 10, lines 64-67; col. 11, lines 1-23).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the automated transformation system of Unger et al. in the method of Pati et al. and Bylina et al. The motivation to do so, provided by Unger et al., would have been that "the invention described herein has utility for genomics library screening, large-scale transfection of cells, and other specialized operations where the ability to achieve high levels of transfection in a short time and in high quantity is desirable." (col. 2, lines 37-41).

10. Claims 12, 33 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pati et al. (U.S. Patent No. 6,524,856; cited in the previous office action) and Georgiou et al. (Nature Biotechn., vol. 15, pp. 29-34, 1997).

A) Regarding claim 12, Pati et al. teach a method for targeting sequence modifications in a family of genes using homologous recombination (Abstract). In particular, Pati et al. teach a method comprising the steps

a) providing a plurality of enhanced homologous recombination (EHR) compositions, wherein each composition comprises:

i) a recombinase (Pati et al. teach coating of double stranded (ds) DNA probes with recombinase (Fig. 2; col. 8, lines 1-3; col. 12, lines 32-36; col. 16, lines 16-37));

ii) a first and a second targeting polynucleotide, wherein said first targeting polmucleotide comprises a portion substantially complementary to a fragment of a target nucleic acid and is substantially complementary to said second targeting polynucleotide (Pati et al. teach a plurality of EHR compositions comprising target nucleic acids from a mixture of nucleic acids, two-single stranded targeting polynucleotides which are substantially complementary to each other and each has a homology clamp (= a portion substantially complementary to a fragment of a target nucleic acid) for target nucleic acids from a gene family; see col. 4, lines 31-37; col. 13, lines 11-16 and 35-45; col. 14, lines 15-21 and 64-67); and

iii) a separation moiety (Pati et al. teach targeting polynucleotides with attached purification tags; see col. 4, lines 37-42;col. 23, lines 9-14; col. 26, lines 1-13);

b) contacting said EHR compositions with a library of target nucleic acid(s) under conditions wherein said targeting polynucleotides hybridize to one or more target nucleic acids of said library (Pati et al. teach contacting EHR compositions with a library of target nucleic acids; see Fig. 2; col. 30, lines 1-5); and

c) isolating and cloning said target nucleic acid(s) (Pati et al. teach isolation of the target nucleic acids by binding biotin to targeting polynucleotides and isolating target nucleic acid:

targeting polynucleotide complex using streptavidin-coated magnetic beads and cloning of the isolated genes (Fig. 2; col. 23, lines 9-14; col. 25, lines 52-58; col. 26, lines 1-13).).

B) Pati et al. teach that the recombination composition can be used for cloning of genes (col. 25, lines 50, 51), creating pools of libraries of variant nucleic acid sequences and cellular libraries containing the variant libraries (col. 26, lines 24-30). Pati et al. teach identification of colonies which contain the desired inserts (col. 30, lines 6-14). Pati et al. teach screening of target cells based on phenotypic, biochemical, genotypic or other functional changes (col. 29, lines 22-29). Pati et al. do not teach using a robotic system for isolating and cloning target nucleic acids, where the system comprises a computer processor programmed to manipulate a device comprising at least one of a cell sorter.

C) Georgiou et al. teach screening of polypeptide libraries displayed on the surface of bacterial cells by FACS (fluorescence activated cell sorting). The cell libraries are constructed by expressing shrt peptides within surface proteins of Gram-negative bacteria (page 29, second paragraph) or yeast (page 30, fifth paragraph). The resulting cell surface displayed libraries can be screened by FACS for high throughput screening (page 30, paragraphs 9-11; page 31, paragraphs 1-3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used fluorescence activated cell sorter of Georgiou et al. for screening of transformed cells of Pati et al. The motivation to do so, provided by Georgiou et al., would have been that cell sorting provided high enrichment ratio of positive clones and was able to discriminate directly between binder of different specificity and affinity, and the enrichment factors were as high as 10,000:1 per round of selection. Further, FACS allowed screening of peptide libraries in different microorganisms (page 30, tenth paragraph).

11. Claims 12, 33 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pati et al. (U.S. Patent No. 6,524,856; cited in the previous office action) and Dunlay et al. (U.S. Patent No. 5,989,835).

A) Regarding claim 12, Pati et al. teach a method for targeting sequence modifications in a family of genes using homologous recombination (Abstract). In particular, Pati et al. teach a method comprising the steps

a) providing a plurality of enhanced homologous recombination (EHR) compositions, wherein each composition comprises:

i) a recombinase (Pati et al. teach coating of double stranded (ds) DNA probes with recombinase (Fig. 2; col. 8, lines 1-3; col. 12, lines 32-36; col. 16, lines 16-37));

ii) a first and a second targeting polynucleotide, wherein said first targeting polmucleotide comprises a portion substantially complementary to a fragment of a target nucleic acid and is substantially complementary to said second targeting polynucleotide (Pati et al. teach a plurality of EHR compositions comprising target nucleic acids from a mixture of nucleic acids, two-single stranded targeting polynucleotides which are substantially complementary to each other and each has a homology clamp (= a portion substantially complementary to a fragment of a target nucleic acid) for target nucleic acids from a gene family; see col. 4, lines 31-37; col. 13, lines 11-16 and 35-45; col. 14, lines 15-21 and 64-67); and

iii) a separation moiety (Pati et al. teach targeting polynucleotides with attached purification tags; see col. 4, lines 37-42;col. 23, lines 9-14; col. 26, lines 1-13);

b) contacting said EHR compositions with a library of target nucleic acid(s) under conditions wherein said targeting polynucleotides hybridize to one or more target nucleic acids of said library

(Pati et al. teach contacting EHR compositions with a library of target nucleic acids; see Fig. 2; col. 30, lines 1-5); and

c) isolating and cloning said target nucleic acid(s) (Pati et al. teach isolation of the target nucleic acids by binding biotin to targeting polynucleotides and isolating target nucleic acid: targeting polynucleotide complex using streptavidin-coated magnetic beads and cloning of the isolated genes (Fig. 2; col. 23, lines 9-14; col. 25, lines 52-58; col. 26, lines 1-13).).

B) Pati et al. teach that the recombination composition can be used for cloning of genes (col. 25, lines 50, 51), creating pools of libraries of variant nucleic acid sequences and cellular libraries containing the variant libraries (col. 26, lines 24-30). Pati et al. teach identification of colonies which contain the desired inserts (col. 30, lines 6-14). Pati et al. teach screening of target cells based on phenotypic, biochemical, genotypic or other functional changes (col. 29, lines 22-29). Pati et al. do not teach using a robotic system for isolating and cloning target nucleic acids, where the system comprises a computer processor programmed to manipulate a device comprising at least one of a fluorescence microscope.

C) Dunlay et al. teach screening of fluorescently labeled cells for interaction with compounds of potential biological activity (Abstract). Dunlay et al. teach computer-controlled scanning of an array of microplate locations containing cells with a fluorescent microscope after the cells have been contacted with reagents (col. 3, lines 8-33; Fig. 1

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used fluorescence microscope of Dunlay et al. for screening of transformed cells of Pati et al. The motivation to do so, provided by Dunlay et al., would have been that the system allowed rapid determination of the distribution, environment and activity of fluorescently labeled

molecules in the cell for the purpose of screening large numbers of compounds that specifically affect particular biological function.

12. No claims are allowed.

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS
May 6, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER